Bridged Bicyclic γ-Sultams by Intramolecular Flow Photochemical [2+2] Cycloaddition

Yevhen O. Zaika,[a,b] Illia O. Borodin,[a,c] Heorhii O. Olekh,[a,c] Maksym V. Kovalov,[a,c] Oleksandr D. Diachenko,[a,c] Volodymyr S. Brovarets,[b] Bohdan V. Vashchenko,[a,c] Oleksandr O. Grygorenko[a,c]*

[a] Enamine Ltd, 78 Winston Churchill St, Kyiv 02094, Ukraine
[b] V. P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, 1 Akademik Kukhar St, Kyiv 02094, Ukraine
[c] Taras Shevchenko National University of Kyiv, 60 Volodymyrska St, Kyiv 01601, Ukraine; gregor@univ.kiev.ua

Dedicated to the memory of Viktor Vashchenko

Abstract: An elegant synthetic approach to the construction of a novel saturated heterocycle – 2-thia-3-azabicyclo[2.1.1]hexane 2,2-dioxide – was designed. The key step included intramolecular flow photochemical [2 + 2] cycloaddition of appropriately substituted dienes, in turn obtained from readily available starting materials on a multigram scale. Further synthetic transformations of the resulting bicyclic compounds enabled preparation of numerous functionalized derivatives useful for early drug discovery programs as promising isosteres of pyrrolidine, pyrrolidone, and γ-sultams, and also demonstrated tolerance of the title bicyclic system towards typical organic chemistry reaction conditions.

1. Introduction

Cyclic sulfonamides, also known as sultams, have found diverse applications in drug discovery (e.g., the anticonvulsant sultiame or the antimicrobial taurolidine, as well as numerous leads and drug candidates), asymmetric synthesis (e.g., camphorsultam as a chiral auxiliary), agricultural and food chemistry (e.g., the artificial sweetener saccharin), and other areas.[1–4] Taking into account the well-known non-classical isosterism of sulfonamide and carboxamide moieties,[5,6] sultams can be considered as three-dimensional mimetics of lactams (Figure 1, *A*). On the other hand, sultams can be also regarded as isosteres of saturated heterocyclic amines, which lack basicity at the physiological conditions but still retain capability of chemical modification at the NH moiety through its increased acidity.

Imposing conformational restriction through a bicyclic system is an important design methodology in drug discovery that can improve the compound's potency, selectivity, physicochemical and/or metabolic profile, and this approach was implemented successfully for numerous bicyclic sultams.[7] For the smallest representatives of the series, however, the above strategy may represent a considerable synthetic challenge. Such rigidification is well-studied for saturated heterocyclic amines (i.e., pyrrolidine) and to a lesser extent – for γ-lactams (Figure 1, *B*). Thus, 2,4-methanoproline (**1**) was isolated from natural sources as early as in 1980.[8] Since then, numerous efficient approaches to the synthesis of 2,4-methanopyrrolidines were developed.[9–17] Meanwhile, isosteric bridged bicyclic γ-sultam, 2-thia-3-azabicyclo[2.1.1]hexane 2,2-dioxide (**2**), remained unknown to date. Recently, we have reported the preparation of its isomer – 2-thia-1-azabicyclo[2.1.1]hexane 2,2-dioxide (**3**), the smallest "Paquette's sultam".[18]

We anticipated that bicyclic system **4** could be constructed in an efficient and atom-economy manner through intramolecular photochemical [2 + 2] cycloaddition of appropriately substituted diene **5** (Scheme 1, *A*). Notably, intramolecular photochemical [2 + 2] cycloaddition was used to construct fused bicyclic sultams previously (Scheme 1, *B*);[19] its application for the synthesis of bridged bicyclic systems was hereto unknown. Nevertheless, we have been inspired by the fact that a similar method was used to obtain 2,4-methanoproline **1** and other 2,4-methanopyrrolidines (Scheme 1, *C*).[9, 11,20–24]

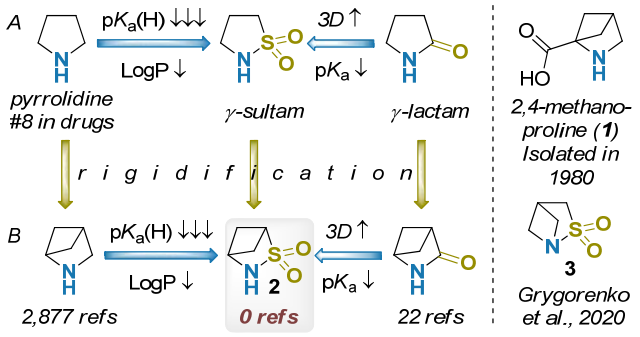
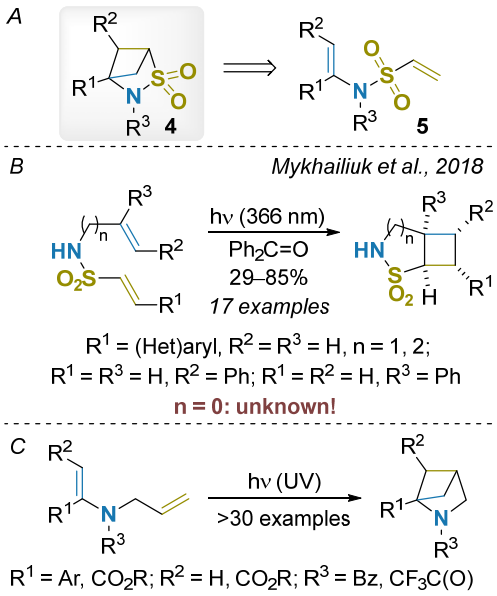
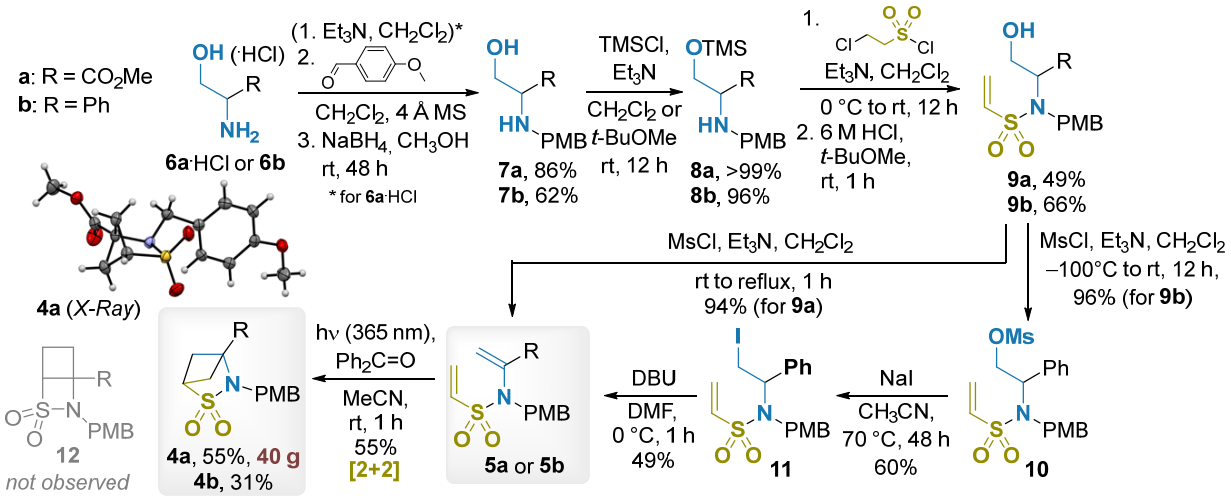


Figure 1. Design of the target bicyclic system (numbers of references according to *Reaxys*® database, accessed on Sep 03, 2024).



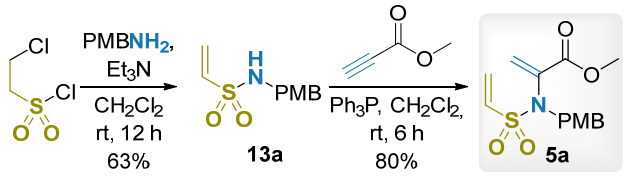
Scheme 1. Synthesis of bicyclic sultams by intramolecular photochemical [2+2] cycloaddition (relative configurations are shown)

Based on these literature precedents, we have chosen intermediates **5a** and **5b** bearing an ester synthetic handle and phenyl substituent, respectively, for the preparation of target 2-thia-3-azabicyclo[2.1.1]-hexane 2,2-dioxides. Compound **5a** could be prepared on a large scale (over 100 g in a single run) in 39% overall yield starting from readily available serine methyl ester hydrochloride (**6a**) (Scheme 2). For intermediate **5b**, somewhat longer reaction sequence was required due to the complications at the diene formation step. The key step – [2+2] cycloaddition – was performed by passing a highly diluted solution of **5a** or **5b** in MeCN (c = 16 mM) through a flow photoreactor upon irradiation at 365 nm in the presence of benzophenone at rt for 1 h. The cycloaddition was accompanied by polymerization, and after some optimization, we could achieve 55% yield of target product **4a** on up to 40 g scale. As might be anticipated, the reaction was less efficient for the case of **5b**, so that product **4b** was obtained in 32% yield. Formation of fused regioisomers **12** was not observed at these conditions. The structure of sultam **4a** was confirmed by X-Ray diffraction studies.



Scheme 2. Synthesis of sultams **4a** and **4b** (PMB – *p*-methoxybenzyl).

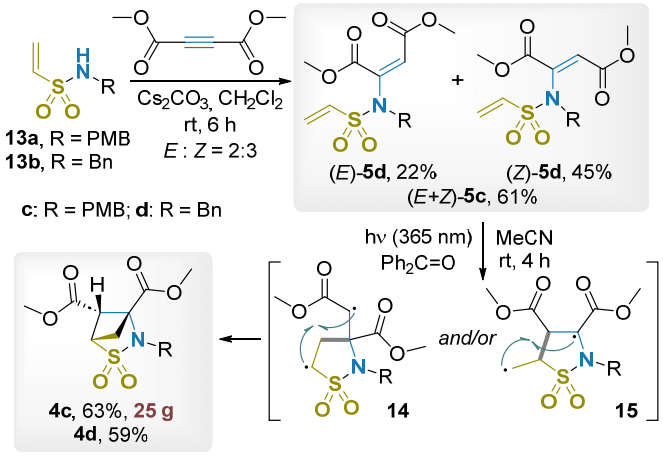
We have tried to improve the above reaction sequence by implementing a much shorter approach to the synthesis of diene **5a** (Scheme 3). Thus, 2-chloroethane-1-sulfonyl chloride was subjected to the reaction with *p*-methoxybenzylamine ($PMBNH_2$) in the presence of Et_3N to give vinyl sulfonamide **13** (63% yield). Further PPh_3-mediated α-Umpolung addition of compound **13** to methyl propiolate[25] proceeded smoothly to give required intermediate **5a** in 80% yield. However, these yields were reproducible on up to 200-mg scale and quickly diminished upon further scale-up attempt. Therefore, this alternative method can be useful for the rapid production of cycloadducts **4** in relatively small quantities.



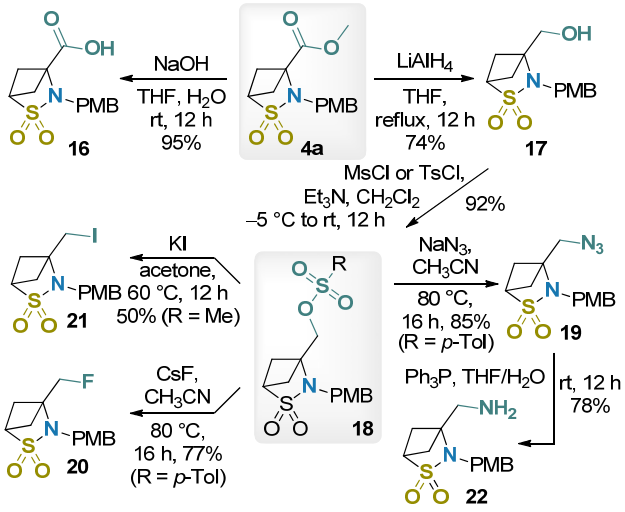
Scheme 3. Alternative synthesis of diene **5a**.

Nevertheless, a similar approach worked well for the preparation of dienes **5c** and **5d** (Scheme 4). This diene intermediates were obtained in 61–67% yield as mixtures of *E* and *Z* isomers (ca. 2:3 ratio). In the case of **5d**, this mixture was separated by column chromatography (22% and 45% isolated yields, respectively). Notably, the subsequent flow photochemical [2 + 2] cycloaddition reaction of either isomer (*E*)- or (*Z*)-**5d** (or mixture thereof) gave cycloadduct **4d** as a single diastereomer (59% yield). These results suggest non-synchronous biradical mechanism for the cycloaddition step, with possible formation of intermediates **14** and/or **15**. Starting from a mixture of (*E*)- or (*Z*)-**5c**, compound **4c** was obtained in 63% yield. Notably, the latter step could be performed on up to 25 g scale in a single run without considerable changes in the reaction outcome.

Since we have shown previously that 2-thia-1-azabicyclo[2.1.1]hexane derivative **3** is prone to ring system opening, we wanted to find out if compounds **4a–c** tolerate typical organic transformations, as well as use the ester synthetic handle in its molecule to obtain a series of building blocks relevant to medicinal chemistry. These included reactions of ester **4a** with strong nucleophilic agents such as alkali (providing carboxylic acid **16** in 95% yield) or $LiAlH_4$ (giving primary alcohol **17** in 74% yield); transformation of compound **17** into sulfonates **18** and their further S_N2 reactions with azide, fluoride, or iodide (albeit in the latter case, corresponding product **21** was obtained in moderate yield due to its limited stability), as well as Staudinger reduction of azide **19** into primary amine **22** (Scheme 5). Moreover, Weinreb amide **23** could be obtained from carboxylic acid **16** in 49% yield, and the bicyclic sultam core tolerated further reactions with MeMgBr or PhMgBr (Scheme 6).



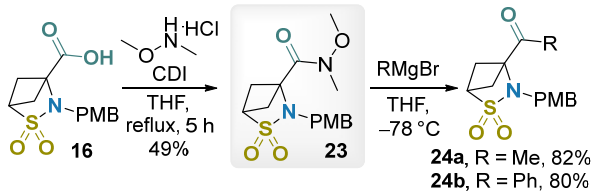
Scheme 4. Synthesis of sultam **4c**.



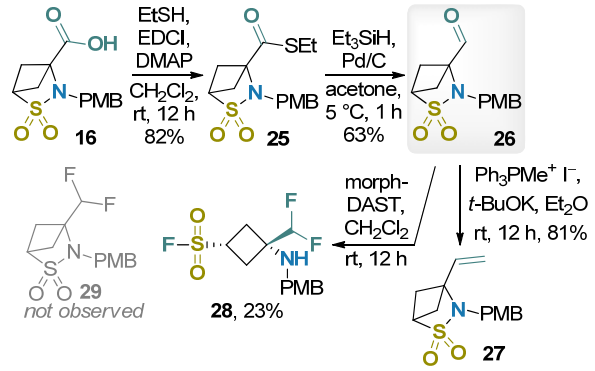
Scheme 5. Reactions of 2-thia-1-azabicyclo[2.1.1]hexane 2,2-dioxide derivatives with nucleophilic reagents.

In addition to that, we synthesized aldehyde **26** via catalytic reduction of thioester **25** (52% yield over two steps), and it was compatible with the Wittig reaction conditions (providing alkene **27**

in 81% yield) (Scheme 7). Meanwhile, deoxofluorination of compound **26** was accompanied by the sultam ring opening. We managed to isolate sulfonyl fluoride **28** in 23% yield from the reaction mixture, while target product **29** was not observed.

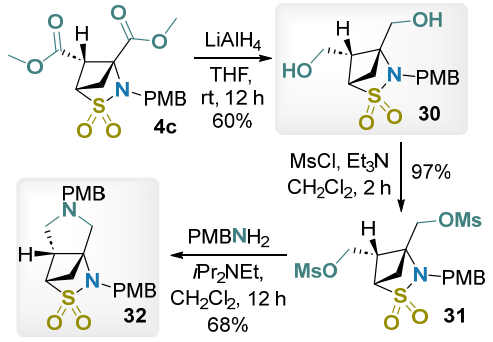


Scheme 6. Preparation of Weinreb amide **23** and its reactions with organometallic reagents.



Scheme 7. Preparation and synthetic transformations of aldehyde **26**.

Synthetic transformations of diester **4c** included its reduction with $LiAlH_4$ giving diol **30** (60% yield) that was transformed into interesting tricyclic pyrrolidine derivative **32** via double mesylation (97% yield) and further amination with *p*-methoxybenzylamine (68% yield) (Scheme 8).



Scheme 8. Synthesis of tricyclic compound **32**.

In conclusion, intramolecular flow photochemical [2 + 2] cycloaddition is a very straightforward and efficient approach to the multigram preparation of 2-thia-3-azabicyclo[2.1.1]hexane 2,2-dioxides. This scaffold is the smallest possible bridged sultam containing carbon atoms at the bridgehead positions and a promising isostere of pyrrolidine, pyrrolidone, and monocyclic γ-sultams. The title bicyclic ring system tolerates many typical organic reaction conditions, including alkaline ester hydrolysis, reduction with $LiAlH_4$, reactions with organometallic reagents, etc., although it is unstable towards certain reagents like Morph-DAST. Therefore, the 2-thia-3-azabicyclo[2.1.1]hexane 2,2-dioxide scaffold can be easily decorated with various functional groups, thus providing valuable chemotypes for early drug discovery programs.

Acknowledgements

The work was funded by Enamine Ltd. The authors thank Vadym Sham and his group for their help with flow experiments, Prof. Dr. Andriy Tolmachov for his encouragement and support, and all the people of Ukraine for making this study possible.

References

(1) Debnath, S.; Mondal, S. Sultams: Recent Syntheses and Applications. *Eur. J. Org. Chem.* **2018**, 933–956.

(2) Mondal, S.; Malakar, S. Synthesis of Sulfonamide and Their Synthetic and Therapeutic Applications: Recent Advances. *Tetrahedron* **2020**, *76*, 131662.

(3) Chong, Y. K.; Ong, Y. S.; Yeong, K. Y. Unveiling Sultam in Drug Discovery: Spotlight on the Underexplored Scaffold. *RSC Med. Chem.* **2024**, *15*, 1798–1827.

(4) Okwuchukwu, P. M.; Bandyopadhyay, D. Medicinally Privileged Sultams: Synthesis and Mechanism of Action. *Mini-Reviews Med. Chem.* **2020**, *20*, 2193–2206.

(5) Meanwell, N. A. Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design. *J. Med. Chem.* **2011**, *54*, 2529–2591.

(6) Meanwell, N. A. Applications of Bioisosteres in the Design of Biologically Active Compounds. *J. Agric. Food Chem.* **2023**, *71*, 18087–18122.

(7) Grygorenko, O. O.; Vashchenko, B. V.; Blahun, O. P.; Zhersh, S. Saturated Bicyclic Sultams. *Eur. J. Org. Chem.* **2020**, No. 36, 5787–5800.

(8) Bell, E. A.; Qureshi, M. Y.; Pryce, R. J.; Janzen, D. H.; Lemke, P.; CIardy, J. 2,4-Methanoproline (2-Carboxy-2,4-Methanopyrrolidine) and 2,4-Methanoglutamic Acid (1-Amino-1,3-Dicarboxycyclobutane) in Seeds of Ateleia Herbert Smithii Pittier (Leguminosae). *J. Am. Chem. Soc.* **1980**, *102*, 1409–1412.

(9) Hughes, P.; Martin, M.; Clardy, J. Synthesis of 2,4-Methanoproline. *Tetrahedron Lett.* **1980**, *21*, 4579–4580.

(10) Homon, A. A.; Hryshchuk, O. V.; Mykhailenko, O. V.; Vashchenko, B. V.; Melnykov, K. P.; Michurin, O. M.; Daniliuc, C. G.; Gerus, I. I.; Kovtunenko, V. O.; Kondratov, I. S.; Grygorenko, O. O. 4-(Di-/Trifluoromethyl)-2-Heterabicyclo[2.1.1]Hexanes: Advanced Fluorinated Phenyl Isosteres and Proline Analogues. *Eur. J. Org. Chem.* **2021**, *2021*, 6580–6590.

(11) Levterov, V. V.; Michurin, O.; Borysko, P. O.; Zozulya, S.; Sadkova, I. V.; Tolmachev, A. A.; Mykhailiuk, P. K. Photochemical In-Flow Synthesis of 2,4-Methanopyrrolidines: Pyrrolidine Analogues with Improved Water Solubility and Reduced Lipophilicity. *J. Org. Chem.* **2018**, *83*, 14350–14361.

(12) Cox, B.; Zdorichenko, V.; Cox, P. B.; Booker-Milburn, K. I.; Paumier, R.; Elliott, L. D.; Robertson-Ralph, M.; Bloomfield, G. Escaping from Flatland: Substituted Bridged Pyrrolidine Fragments with Inherent Three-Dimensional Character. *ACS Med. Chem. Lett.* **2020**, *11*, 1185–1190.

(13) Rammeloo, T.; Stevens, C. V. A New and Short Method for the Synthesis of 2,4-Methanoproline. *Chem. Commun.* **2002**, *2*, 250–251.

(14) Tkachenko, A. N.; Radchenko, D. S.; Mykhailiuk, P. K.;

Grygorenko, O. O.; Komarov, I. V. 4-Fluoro-2,4-Methanoproline. *Org. Lett.* **2009**, *11*, 5674–5676.

(15) Rammeloo, T.; Stevens, C. V.; De Kimpe, N. Synthesis of 2,4-Methanoproline Analogues via an Addition-Intramolecular Substitution Sequence. *J. Org. Chem.* **2002**, *67*, 6509–6513.

(16) Krow, G. R.; Lin, G.; Herzon, S. B.; Thomas, A. M.; Moore, K. P.; Huang, Q.; Carroll, P. J. Convenient Preparations of 2,4-Methanopyrrolidine and 5-Carboxy-2,4-Methanopyrrolidines. *J. Org. Chem.* **2003**, *68*, 7562–7564.

(17) Hughes, P.; Clardy, J. Total Synthesis of Cyclobutane Amino Acids from Atelia Herbert Smithii. *J. Org. Chem.* **1988**, *53*, 4793–4796.

(18) Blahun, O. P.; Rozhenko, A. B.; Rusanov, E.; Zhersh, S.; Tolmachev, A. A.; Volochnyuk, D. M.; Grygorenko, O. O. Twisting and Turning the Sulfonamide Bond: A Synthetic, Quantum Chemical, and Crystallographic Study. *J. Org. Chem.* **2020**, *85*, 5288–5299.

(19) Dibchak, D.; Shcherbacova, V.; Denisenko, A. V.; Mykhailiuk, P. K. Convenient Access to Conformationally Rigid Sultams. *Org. Lett.* **2019**, *21*, 8909–8914.

(20) Elliott, L. D.; Berry, M.; Harji, B.; Klauber, D.; Leonard, J.; Booker-Milburn, K. I. A Small-Footprint, High-Capacity Flow Reactor for UV Photochemical Synthesis on the Kilogram Scale. *Org. Process Res. Dev.* **2016**, *20*, 1806–1811.

(21) Elliott, L. D.; Booker-Milburn, K. I. Photochemically Produced Aminocyclobutanes as Masked Dienes in Thermal Electrocyclic Cascade Reactions. *Org. Lett.* **2019**, *21*, 1463–1466.

(22) Lorthioir, O.; Demanze, S.; Nassoy, A. C. Blue Light Enabled Access to Novel (Hetero)Aromatic Bridged Pyrrolidine Alcohols. *Tetrahedron Lett.* **2022**, *108*, 154129.

(23) Varnes, J. G.; Lehr, G. S.; Moore, G. L.; Hulsizer, J. M.; Albert, J. S. Efficient Preparation of 2,4-Methanoproline. *Tetrahedron Lett.* **2010**, *51*, 3756–3758.

(24) Wright, B. A.; Matviitsuk, A.; Black, M. J.; García-Reynaga, P.; Hanna, L. E.; Herrmann, A. T.; Ameriks, M. K.; Sarpong, R.; Lebold, T. P. Skeletal Editing Approach to Bridge-Functionalized Bicyclo[1.1.1]Pentanes from Azabicyclo[2.1.1]Hexanes. *J. Am. Chem. Soc.* **2023**, *145*, 10960–10966.

(25) Fan, Y. C.; Kwon, O. Advances in Nucleophilic Phosphine Catalysis of Alkenes, Allenes, Alkynes, and MBHADs. *Chem. Commun.* **2013**, *49*, 11588–11619.